Coagulopathy by Hypothermia and Acidosis: Mechanisms of Thrombin Generation and Fibrinogen Availability

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Background: Although the lethal triad of hypothermia, acidosis, and coagulopathy has been recognized for a decade, the underlying mechanisms related to the development of coagulopathy are not fully understood. Consequently, current strategy in treating trauma patients with coagulopathy is limited to "staying out of the trouble" instead of "getting out of trouble." A better understanding of the underlying mechanisms will facilitate the search for effective therapeutic approaches when this lethal triad cannot be avoided.
Methods: Reviewing recent studies that explored alterations of thrombin generation and fibrinogen availability caused by hypothermia and acidosis.
Results: Hypothermia and acidosis compromise thrombin-generation kinetics via different mechanisms. Hypothermia primarily inhibits the initiation phase, whereas acidosis severely inhibits the propagation phase of thrombin generation. Similarly, hypothermia and acidosis affect fibrinogen metabolism differently. Hypothermia inhibits fibrinogen synthesis, whereas acidosis accelerates fibrinogen degradation, leading to a potential deficit in fibrinogen availability. In addition, coagulation complications caused by acidosis cannot be immediately corrected by pH neutralization alone.
Conclusions: Hypothermia and acidosis impair thrombin generation and fibrinogen availability via different mechanisms. Current data indicate that pH correction alone cannot immediately correct acidosis-induced coagulation impairments. Future studies are warranted to test the effects of pH neutralization in conjunction with fibrinogen supplementation in normalizing acidosis-induced clotting complications.

Coagulopathy after trauma has been recognized as part of the lethal triad of hypothermia, acidosis, and coagulopathy.[1,2] It is considered to be attributed to dilution from massive blood transfusion, fluid resuscitation, progressive hypothermia, and development of acidosis.[1] The detrimental effects of hypothermia and acidosis are demonstrated in the high-mortality rates of trauma patients, despite resuscitation and an adequate supply of blood, plasma, and platelets.[3,4] This review discusses the recent findings that have been made

concerning alterations of thrombin generation and fibrinogen availability after hypothermia and acidosis.

Thrombin Generation

Coagulation is a complex process with interactions of various procoagulation proteins, platelets, phospholipids, and anticoagulation enzymes. The essence of blood coagulation is the production of fibrin from fibrinogen, and thrombin plays a central role in the process as a catalytic enzyme.[5] A simplified diagram of the coagulation process is shown in Figure 1. Thrombin is generated from precursor prothrombin via the initiation and the propagation phases. In the initiation phase, small amounts of thrombin are produced by the activation of factor VIIa (FVIIa)/tissue factor (TF) complex and factor Xa. Afterward, there is a propagation phase with generation of large amounts of thrombin, which resulted from the production of prothrombinase complex on the surface of activated platelets. A graphic presentation of thrombin generation is shown in Figure 2. The roles of platelet activation and intracellular signaling on thrombus formation have been reviewed recently.[6,7] At the same time, thrombin generation is subject to inhibition from antithrombin III, thrombomodulin-activated protein C, and TF pathway inhibition. This complex mechanism enables rapid clot formation on tissue injury, but inhibition of clot formation away from the site of the injury. Because of the fact that multiple enzymatic reactions are involved in thrombin generation, it is apparent that thrombin generation is thermally regulated.

In coagulation studies, swines are being selected as the experimental model because their cardiovascular system is close to that of humans.[8,9] They are large enough to be instrumented relatively easily and to allow repeated blood samplings. Coagulation and hemorrhage models in swines are based on concepts and procedures developed previously in other animals, particularly the dog; yet, they are superior to canine models because they are more applicable to human-oriented physiologic phenomena and human clinical problems.[8] It should be pointed out that although the use of anesthesia reduces variability between animals by reducing behavioral responses (i.e., excitation to hemorrhage), anesthesia makes the animals less tolerant to blood loss[10] and its effects on the coagulation process are unclear.

The inhibitory effects of hypothermia and acidosis on coagulation enzyme activities and platelet function have been shown in in vitro studies.[11–14] The contributions to thrombin generation from hypothermia and acidosis induced in vivo are revealed recently by Martini et al.[15] Using a swine model

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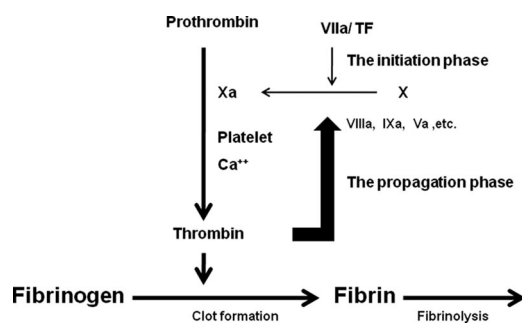| 16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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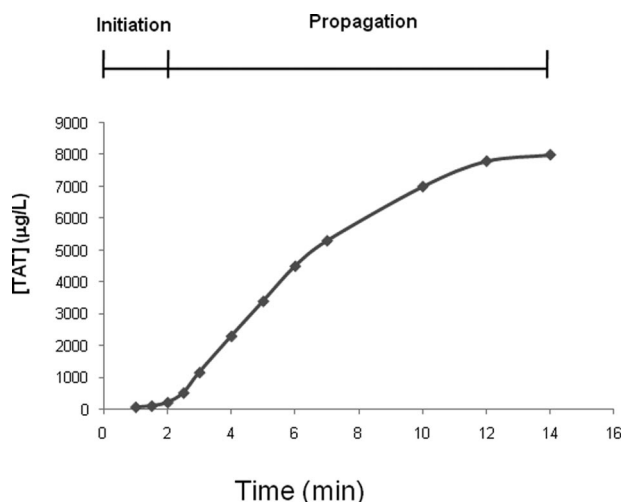**Figure 1.** A simplified diagram of the coagulation process.

Figure 2. A graphical presentation of thrombin generation in the coagulation process.

with four animal groups (control, hypothermia, acidosis, and combined hypothermia and acidosis), Martini et al.[15] investigated the independent and combined effects of hypothermia and acidosis on thrombin-generation kinetics. In this study, hypothermia of 32°C was induced using a cold-water blanket with 4°C circulating water and acidosis of pH 7.1 was induced by the infusion of 0.2 mol/L hydrochloric acid. When target pH and/or temperature were achieved and stabilized for 15 minutes in these animals, blood samples were taken to analyze thrombin-generation kinetics following the procedures described by Rand et al.[16] Data from this study demonstrated that both hypothermia and acidosis impair thrombin generation.[15] Further, hypothermia and acidosis have differential inhibitory effects on thrombin generation.[15] Hypothermia of 32°C primarily caused a delay in the onset of thrombin generation with no significant effects in the propagation phase of thrombin generation[15] (Fig. 3), indicating that the inhibition of hypothermia was primarily located in the FVIIa/ tissue factor pathway. Conversely, acidosis of pH 7.1 moderately inhibited thrombin generation in the initial phase. However, thrombin generation in the propagation phase was persistently and dramatically inhibited by acidosis[15] (Fig. 3), indicating severe inhibition of acidosis in the activation of FV, FVIII, FIX, FX, and formation of FXase and prothrombinase complex.[5]

Findings from the study of Martini et al.[15] provide possible explanations for the clinical observation that rFVIIa is not effective in some acidotic trauma patients. Because severe inhibition of acidosis occurs in the propagation phase and FVIIa is not included in the propagation phase, administering rFVIIa cannot release the inhibition of thrombin generation caused by acidosis. Thus, a better alternative in treating patients with acidotic coagulopathy might be to
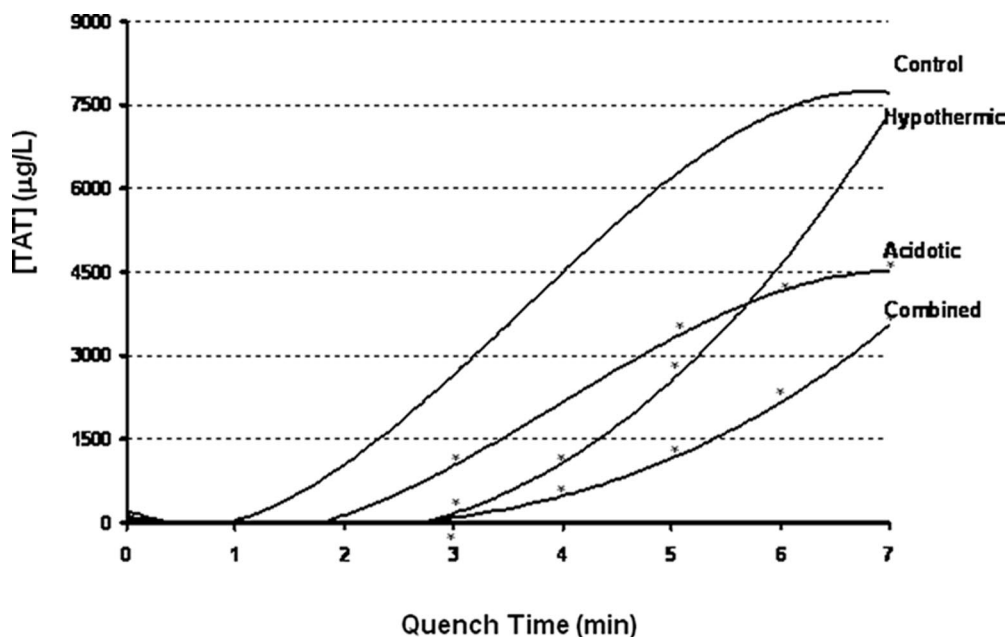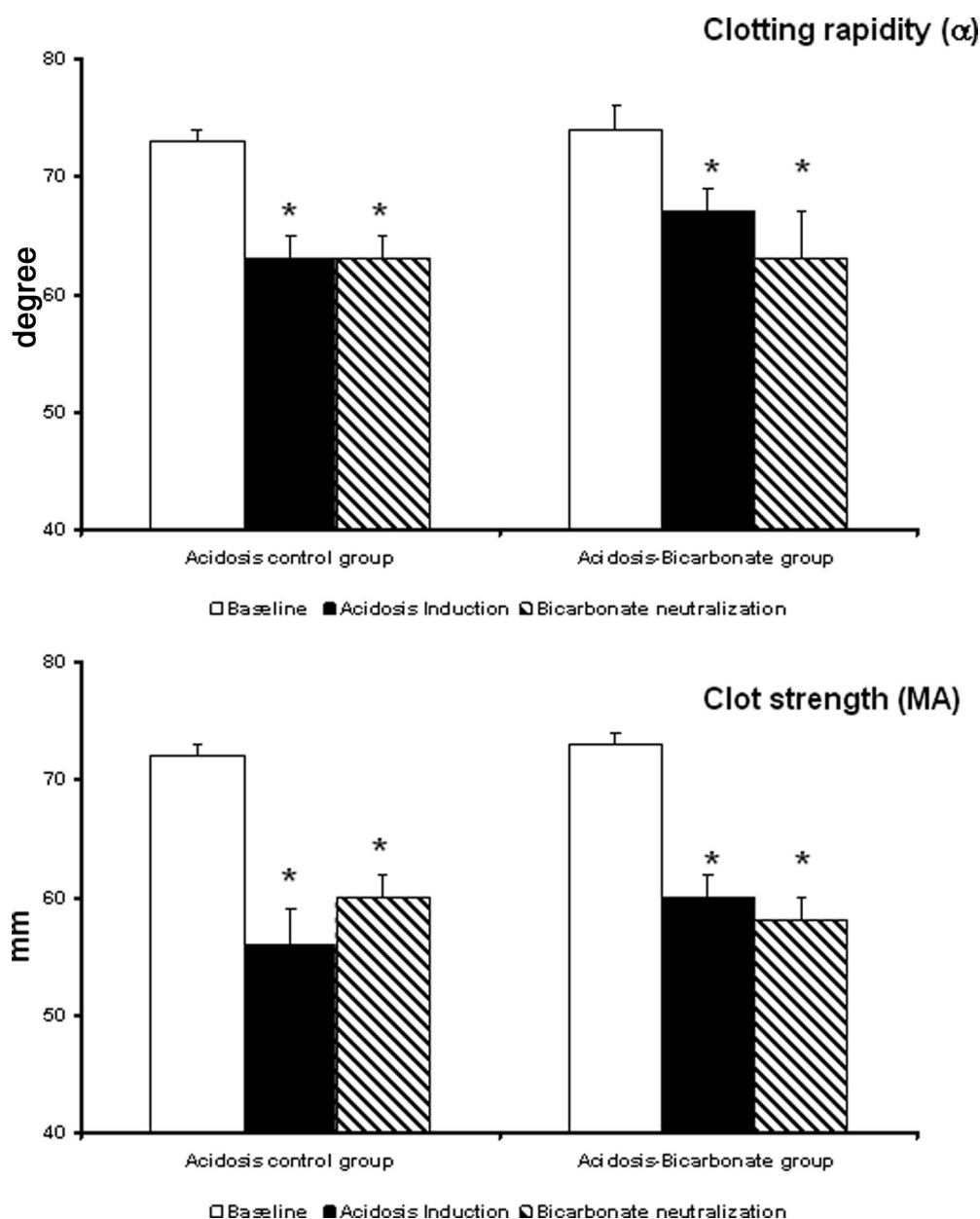

Figure 3. Changes in thrombin-generation kinetics after hypothermia- and acidosis-induced in pigs. Data presented were collected during the study conducted by Martini et al.[15] *$p < 0.05$ compared with control values.

Figure 4. Changes in clotting rapidity and clot strength (MA) by acidosis induction and pH neutralization by bicarbonate in pigs. Data presented were collected during the study conducted by Martini et al.[17] *$p < 0.05$ compared with baseline values.

administer rFVIIa in conjunction with pH correction. In contrast, improvement may be expected from rFVIIa alone in hypothermia patients, because hypothermia primarily inhibits the activation of the FVIIa/TF complex. In addition, because more severe impairment on coagulation occurred in acidosis, these results suggested that correcting pH should be considered an important strategy in reversing clinical coagulopathy.

pH Neutralization

The detrimental effects of acidosis on coagulation support the notion of pH correction. Clinical acidosis is commonly corrected by administering bicarbonate, a pH-neutralization agent. However, recent studies by Martini et al.[17] showed that

coagulation defects from acidosis were not immediately corrected by pH correction. In a swine model, acidosis of pH 7.1 was induced in 12 pigs more than 233 ± 19 minutes with an inflow of 44.7 ± 3.5 mL/kg of 0.2 mol/L HCl.[17] When the target pH of 7.1 was achieved and stabilized, blood samples were taken for analysis of hemodynamics and coagulation. The coagulation profiles were determined for fresh whole blood using thromboelastography (TEG 5000 Hemostasis Analyzer, Hemoscope, Niles, IL). In the TEG measurements, *R* time (min) is the latency time for initial clot formation; *K* time (min) is the duration from initial detectable clot formation to maximum clot formation; *R* + *K* represents the time for maximum clot formation; angle (α,

degree) measures the rapidity of fibrin build up and cross-linking; and maximum amplitude (MA, mm) represents maximum strength or stiffness of the clot. MA is the results of two contributing components, with the modest contribution of fibrin and the much more significant contribution of platelets. In addition, fibrinolysis is assessed by the measurement of LY_{30} in TEG, which measures the rate of amplitude reduction 30 minutes after MA.

After the acidosis induction and blood sampling, 12 animals were randomized into acidosis-bicarbonate group and acidosis-control group. In the acidosis-bicarbonate group, sodium bicarbonate (0.3 mol/L) was infused at the rate of 0.28 mL/kg/min to neutralize arterial pH from 7.1 to 7.4. In the acidosis-control group, lactated Ringer's (LR) solution was infused at the same rate and duration as the 0.3 mol/L sodium bicarbonate infusion in the acidosis-bicarbonate group. When the target pH of 7.4 was achieved and stable for 15 minutes in the acidosis-bicarbonate group, blood samples were taken again for measurements of hemodynamics and coagulation. Data from this study showed that coagulation function was compromised by acidosis, as indicated by decreased clotting speed and clot strength[17] (Fig. 4). After bicarbonate infusion to return pH to 7.4, there were no improvements in coagulation function altered by acidosis, compared with the group without pH neutralization[17] (Fig. 4). For fibrinolysis, we did not observe significant changes in LY_{30} measurements after acidosis induction or after pH neutralization in the study.[17]

To assess hemodilutional effects on coagulation, six additional animals (as volume-control group) were infused with LR at rates to mimic the infusion pattern of 0.2N HCl fluid in the acidosis-control and acidosis-bicarbonate groups. No changes were observed in the volume-control group in any of the coagulation measurements, indicating that any possible hemodilutional effects on coagulation in the study[17] are likely to be minimal.

Considering the increasing awareness of the complications from bicarbonate administration in certain clinical settings,[18–20] a different pH-neutralization agent, tris-hydroxymethylaminomethane was used in a later study by Martini et al.[21] to investigate the efficacy of pH correction on restoration of coagulation function. Similar results showed that there were no improvements in coagulation function after tris-hydroxymethylaminomethane pH neutralization[21] (Fig. 5). Apparently, coagulation defects caused by acidosis in vivo cannot be immediately reversed by pH neutralization alone.

In search of explanations for the noneffectiveness of pH neutralization, changes in clotting substrates by acidosis and pH neutralization were examined.[17,21] Concurrent to coagulation impairments by acidosis and lack of improvement by pH neutralization, fibrinogen levels and platelet counts were significantly decreased by acidosis and remained at their depleted levels after pH neutralization[17,21] (Figs. 6 and 7). The mechanisms leading to the decrease in platelet counts is not fully understood. Djaldetti et al.[22] showed that when pH dropped below 7.4, platelet internal structure and shape changed to becoming spheres deprived of pseudopodia, suggesting that the structural changes might possibly lead to accelerated
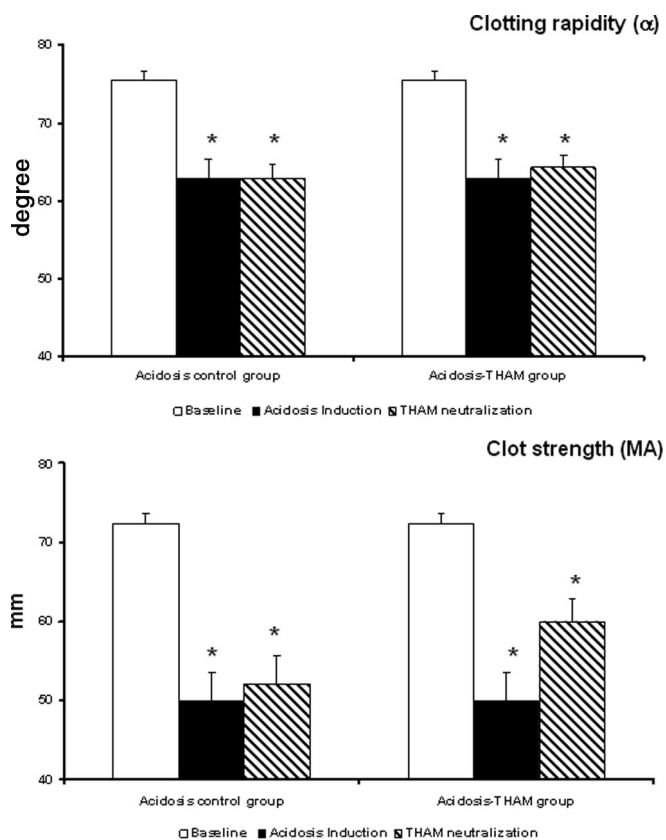
Figure 5. Changes in clotting rapidity and clot strength (MA) by acidosis induction and pH neutralization by tris-hydroxymethylaminomethane in pigs. Data presented were collected during the study conducted by Martini et al.[21] *$p < 0.05$ compared with baseline values.
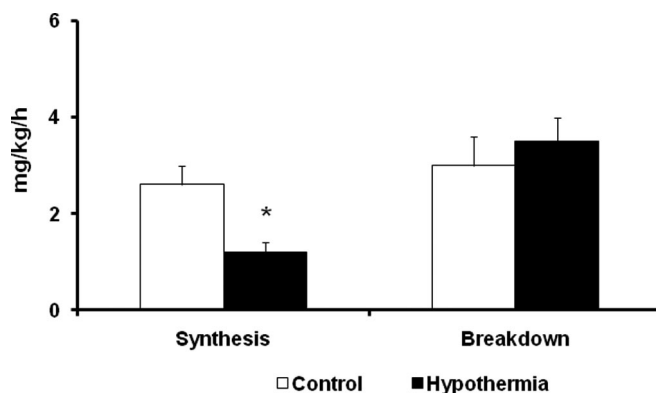
Figure 6. Changes in fibrinogen concentrations and platelet count by acidosis induction and pH neutralization by bicarbonate in pigs. Data presented were collected during the study conducted by Martini et al.[17] *$p < 0.05$ compared with baseline values.

removal of platelet from circulation. In addition, platelet functional impairments by acidosis have been shown in in vitro studies. Marumo et al.[13] reported that platelet aggregation was inhibited by extracellular acidosis of pH 6.9. Similar
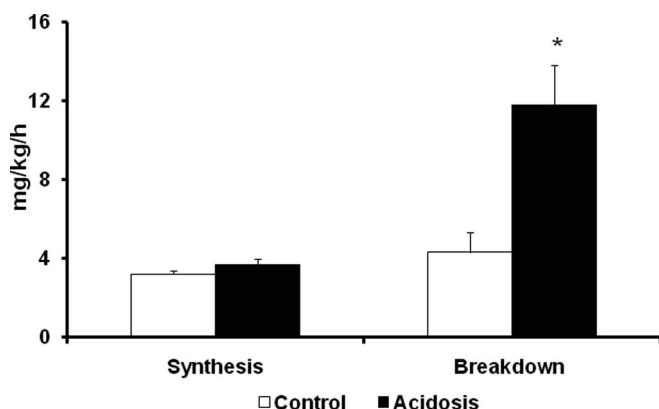
Figure 7. Changes in fibrinogen concentrations and platelet count by acidosis induction and pH neutralization by tris-hydroxymethylaminomethane in pigs. Data presented were collected during the study conducted by Martini et al.[21] *p < 0.05 compared with baseline values.

inhibition of acidosis on platelet aggregation was also shown by Chaimoff et al.[14] The in vivo effects of acidosis on platelet function, however, remain to be investigated. Nevertheless, because fibrinogen and platelets are essential for clotting function, it is possible that the lack of immediate efficacy from pH neutralization may be due to the inability to restore fibrinogen and platelets immediately. In other words, impairment of coagulation function may possibly result from the depletions of substrates. Taken together, these acidosis studies suggest that changes in coagulation are connected to changes in substrates, not pH per se. It is substrate deficiency that leads to coagulation dysfunction during acidosis.

Fibrinogen Availability

Fibrinogen deficiency has been recognized in acutely injured trauma patients. Among all the factors involved in the coagulation process, fibrinogen is found to be the first component to drop to critical levels in patients with coagulation defects.[23–27] The drop is not attributable to blood loss and fluid resuscitation.[25] To reveal the underlying mechanisms related to fibrinogen drop requires a methodology to quantify changes of fibrinogen metabolism in vivo. Recently, Martini et al.[28] developed an in vivo technique to quantify fibrinogen synthesis and degradation. This technique involves the infusion of stable isotope-labeled amino acids and subsequent gas chromatography mass spectrometry analysis.[28] Using different stable isotope-labeled amino acids with different infusion durations, this technique allows simultaneous and independent quantification of fibrinogen synthesis and degradation. The establishment of this technique made it possible to investigate changes in fibrinogen availability under trauma-related circumstances.

The Effects of Hypothermia on Fibrinogen Availability

The association of hypothermia to coagulation dysfunction and mortality has been well described.[4,29–33] The dynamic changes of fibrinogen metabolism during hypothermia were recently revealed by Martini et al.[34] In a normovolemic swine model, hypothermia of 32°C was induced using a cold blanket with circulating water at 4°C.[34] When the animal temperature was lowered to 32°C and stabilized, stable isotope 1-^{13}C-phenylalanine was infused for 6 hours and d5-phenylalanine was infused for 4 hours to investigate changes in fibrinogen synthesis and degradation. Blood samples were taken hourly during the infusion and the isotopic labeling of fibrinogen was determined using gas chromatography and mass spectrometry analysis. Data from this study showed that hypothermia of 32°C decreased fibrinogen synthesis from the control value of 2.6 ± 0.4 mg/kg/h to 1.2 ± 0.2 mg/kg/h ($p < 0.05$), with no effects on fibrinogen degradation[34] (Fig. 8). This observation indicates that in response to cooling, fibrinogen synthesis and degradation are regulated via different mechanisms and also there is a potential deficit in fibrinogen availability after hypothermia.

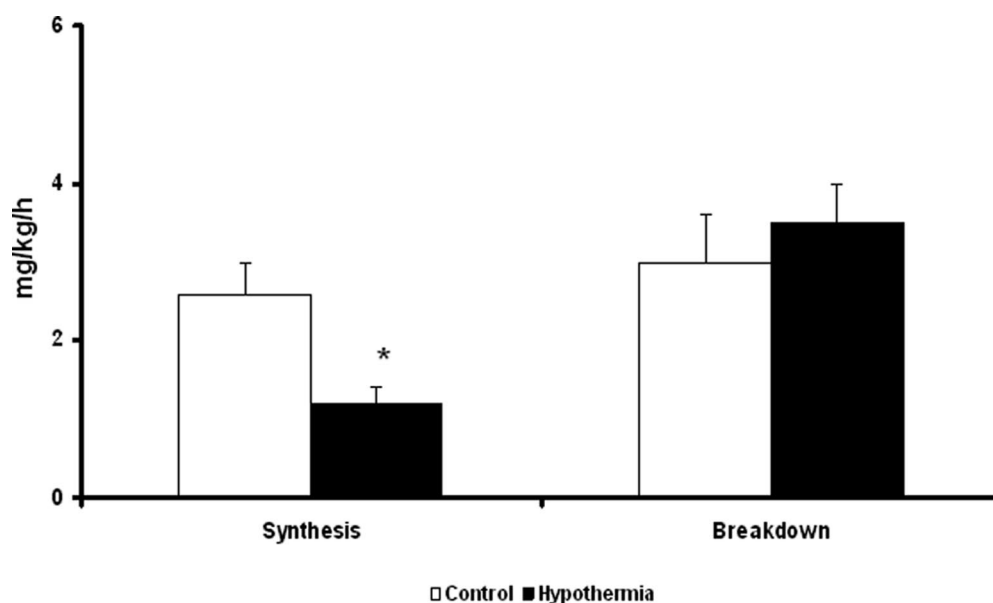### The Effects of Acidosis on Fibrinogen Availability

Among all the factors contributing to coagulation disorders, acidosis is one of the most important predictors of coagulopathy in trauma patients,[3] with the likelihood of death increasing as the severity of acidosis increases.[1,4,35–37] The mechanisms contributing to the depletions of fibrinogen by acidosis were recently reported by Martini et al.[38]

In a swine model, acidosis of pH 7.1 was induced by an infusion of 0.2N HCl in LR.[38] When pH of 7.1 was stabilized, a stable isotope infusion of 1-^{13}C-phenylalanine (for 6 hours) and d5-phenylalanine (for 4 hours) was performed to investigate changes in fibrinogen metabolism. Blood samples were taken hourly during the infusion, followed by subsequent gas chromatograph and mass spectrometry analysis. Data from this study showed that, in contrast to the effects of hypothermia, acidosis increased fibrinogen degradation by 1.8-fold by acidosis compared with control values, with no effects on fibrinogen synthesis[38] (Fig. 9). Thus, it seems that there were differential effects on fibrinogen synthesis and breakdown by acidosis and there was a potential depletion of fibrinogen availability after acidosis.

To summarize, it is clear that hypothermia and acidosis affect fibrinogen synthesis and degradation via different mechanisms. Despite the differential effects, hypothermia and acidosis lead to a consistent outcome: deficit in fibrinogen availability. It should be noted that fibrinogen metabolic changes after trauma might be more complex than the effects from hypothermia or acidosis alone, because of the multifactorial nature of trauma. Nevertheless, findings from hypothermia and acidosis support the notion of fibrinogen supplementation in acutely injured patients with coagulation complications.

Fibrinogen Supplementation

Fibrinogen supplementation of coagulation substrates seemed to be beneficial in animal experiments. In pigs with 60% blood volume exchanged with hydroxyethyl starch, Fries et al.[39] investigated the effects of fibrinogen supplementation with prothrombin complex concentrate on dilutional coagulopathy. The blood loss in the supplement group was 240 mL (50–830 mL) compared with 1,800 mL (1,500–2,500 mL) in the placebo group. All animals survived in the

Figure 8. Effects of hypothermia (32°C) on fibrinogen synthesis and breakdown in pigs. Data presented were collected during the study conducted by Martini et al.[34] *$p < 0.05$ compared with control values.
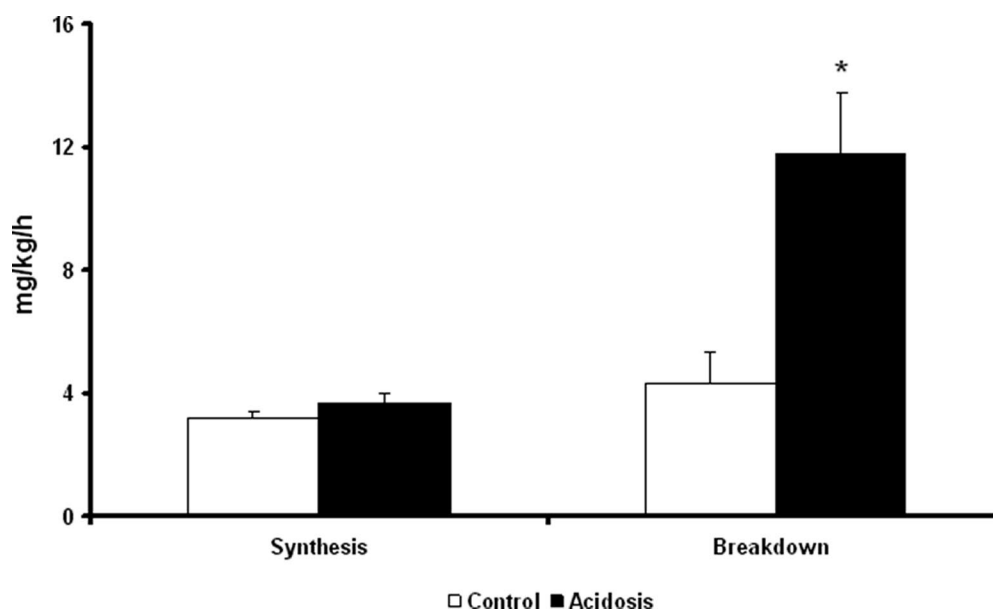
Figure 9. Effects of acidosis (pH 7.1) on fibrinogen synthesis and breakdown in pigs. Data presented were collected during the study conducted by Martini et al.[38] *$p < 0.05$ compared with control values.

supplement group compared with 20% survival in the placebo group.[39] These experimental findings support the approach of using fibrinogen supplementation to correct coagulation complications related to fibrinogen deficiency. However, the threshold of fibrinogen at which bleeding complications provoked is difficult to define, as it depends on the status of hematocrit, platelet, thrombin, platelet function, and clotting enzyme activities. Further, it remains unclear how early supplement of fibrinogen may affect the dynamic features of fibrinogen metabolism.

CONCLUSIONS

Coagulopathy resulting from hypothermia and acidosis is a major contributor to the mortality and morbidity in trauma patients. Recent studies revealed the inhibitory effects of hypothermia and acidosis on thrombin generation and fibrinogen availability. Hypothermia primarily inhibits thrombin generation in the initiation phase, whereas acidosis severely impairs thrombin generation in the propagation phase; and hypothermia inhibits fibrinogen synthesis, whereas acidosis

accelerates fibrinogen degradation, leading to a potential deficit in fibrinogen availability. In addition, current data indicate that pH correction alone cannot immediately correct acidosis-induced coagulation impairments. Future studies are warranted to test the effects of pH neutralization in conjunction with fibrinogen supplementation in normalizing acidosis-induced clotting complications.

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EDITORIAL COMMENT

This timely report by Martini et al. continues their investigation of the complex interactions of hypothermia and acidosis to postinjury coagulopathy, with the ultimate goal being to the elucidation of the mechanisms underlying the bloody vicious cycle, described by our group over 28 years ago.[1] Using a porcine model, the author has shown that hypothermia impairs the initiation phase of thrombin generation, occurring early in the process via down regulation of the VIIa tissue factor complex. In contrast, acidosis was shown to impair thrombin burst providing plausible evidence for the clinical findings of ineffective recombinant VIIa action with acidosis. The author appropriately applied thrombelastography to determine the in vivo effects of pH correction and studied the effects of α angle (clot kinetics) and maximum amplitude for clot strength to assess changes with acidosis.

Using gas chromatography and mass spectrometry analysis, the author suggested that acidosis resulted in enhanced fibrinogen degradation, whereas hypothermia impaired fibrinogen synthesis. She further noted that platelet counts were sig-

nificantly decreased by acidosis and this sequestration was not altered by subsequent pH neutralization.

The author is to be congratulated for her continued efforts to define the contributions of hypothermia and acidosis to the complexities of postinjury coagulopathy. Furthermore, as our group and others have shown,[2–4] thrombelastography appears to be an important monitoring tool, because of its correlation to the cell-based model of coagulation,[5,6] which parallels the various steps initiated by thrombin generation. These processes emphasize that the ultimate goal of resuscitation is the formation of a stable clot, and the physiologic process driving this goal is dynamic rather than static. For example, isolated platelet or fibrinogen deficiency is rarely seen in postinjury coagulopathy, but is part of a dynamic, multifactorial process eventuating in substrate deficiency. Accordingly, the interactions of thrombin, soluble fibrinogen, platelet surface activation, and injured endothelium must be considered in total when studying this process, particularly when extrapolating these studies to clinical resuscitation protocols. For example, the continuum of thrombin kinetics cannot be evaluated in the absence of its interaction with the platelet. Indeed, as the authors have suggested, little is known about in vivo platelet function in the face of acidosis and hypothermia, and their contribution to the stable clot. Furthermore, the clotting system of the swine in the laboratory is clearly different from the severely injured patient with protracted hemorrhagic shock and multiple regions of disrupted endothelium. Nonetheless, continued investigations into mechanisms of coag-

ulation altered by hypothermia and acidosis are essential to improve our understanding of this complex process and are particularly important before clinical trials of presumptive resuscitation strategies.

In summary, we applaud the authors for their pioneering investigations in the cellular basis underlying the contributions of hypothermia and acidosis, and look forward to further studies addressing the dynamic process that leads to the stable clot.

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